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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 08/999,690 | 09/08/1997 | WALTER H. GUNZBURG | GSF97-03A | 4218 |

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| EXAMINER | |
|---|---|
| LI, QIAN J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | 09 |

DATE MAILED: 08/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 08/999,690 | GUNZBURG ET AL. | |
| | Examiner | Art Unit | |
| | Q. Janice Li | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4-23,25-28,30,31,34-40,42-49 and 52-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *9-15,20,22,26,35-40,46-48,52,60-65,70-72 and 75* is/are allowed.

6)☒ Claim(s) *1,2,4-8,16-19,21,23,25,27,28,30,31,34,42-45,49,53-59,66-69,73,74,76 and 77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 May 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some.* c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

The amendment and remarks filed on May 28, 2003 has been entered and assigned as Paper #28. Claims 1, 2, 5, 20, 21, 27, 28, 31, 46, 47, 55, 56, 58, 70, and 71 have been amended. Claims 1, 2, 4-23, 25-28, 30, 31, 34-40, 42-49, 52-77 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5-8, 21, 27, 28, 30, 31, 34, 55-59 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention

is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Specifically, these claims recite "*a recombinant vector*" rather than a recombinant retroviral vector, so that claims are drawn to *any* vector comprising a retroviral vector DNA sequence or a 5' LTR comprising the structure U3-R-U5. However, the only vector adequately described in the original disclosure is a retroviral plasmid vector.. Accordingly, vectors beyond the recombinant retroviral plasmid vector have not been adequately described, and the original disclosure fails to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To the extent that the claimed vectors are not adequately described in the instant disclosure, claims 1, 2, 4, 5-8, 21, 27, 28, 30, 31, 34, 55-59 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been adequately described.

ENABLEMENT REQUIREMENT

Claims 16-19, 23, 25, 42-45, 49, 53, 54, 66-69, 73, 74, 76, and 77 stand rejected under 35 U.S.C. § 112, 1st paragraph. Particularly, the specification, while being enabling for anti-tumor or anti-viral activities *in vitro*, does not reasonably provide enablement for treating any and all diseases selected from the group consisting of a genetic defect, cancer, and viral infections. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

With regard to claims drawn to therapeutic methods, applicants argue in paper #28 that the Examiner has not provided acceptable evidence or reasoning which casts doubt on Applicant's in vivo data, and the Examiner appears to be requiring human data for enablement of the claimed invention. Applicants further indicate that a "not" seems to be missing from one of the sentence of the Office action.

In response, it is acknowledged, that the word "not" is inadvertently missed from the recited sentence. However, the message of the section is clear because it is consistent from the base of the rejection to the conclusion of the section.

With respect to the reasoning of casting doubt on applicant's in vivo data, it has been provided repeatedly in the previous Office actions papers #9, 11, 17, and, in the Office action paper #25, only rebuttal was provided to applicant's argument denying the therapeutic aspect of the invention. The following is some of the reasoning provided in the previous Office actions, particularly regarding the *in vivo* data in the specification and clinical relevance.

Paper#17

The only *in vivo* model system used in the "antitumor experiments" is an immune compromised mice injected with tumor cell line, which transduced with melittin or cecropin and derivatives thereof. The specification recites that these transduced cell-clones show "a reduced rate of tumor growth". However, the incidence of tumor after these cell-line injections shows large variations in figures 9 and 10. Tumor incidence is about *69%* in mice with *control* EJ cells, 100% in Cecropin-A10.8 and two groups of Pre Melittin-6 transduced tumor cells, 87% in Cecropin-A1.7 transduced tumor cells and 88% in Pre Pro Melittin-1 transduced cells, these results are contrary to what is claimed.

Furthermore, the means and ways to treat a *naturally occurred* genetic defect, a tumor or a viral infection, which is essential to the claimed invention, are not disclosed in the specification.

Another important factor needs be considered for therapeutic use is the side effects of these AMPs and derivatives. All AMPs and their derivatives, which have an antimicrobial and antitumor activity, will also have a cytotoxic effect to the host. "THEY AVOID THE PROBLEM OF SELF-DESTRUCTION EITHER BY A CELLULAR COMPARTMENTALIZATION OR BY SPECIFICITY FOR A MICROBIAL TARGET THAT IS ABSENT IN THE ANIMAL HOST" (Boman, pg. 62, 2nd paragraph). When given by a systemic method to a mammal host, the effect to normal cells of the host has to be evaluated. This aspect of claimed invention has not been disclosed by the applicants, therefore, the method is not enabled to use *in vivo* therapeutically.

Paper#20:

In view of the state of the art, the gene therapy for cancer, viral and hereditary diseases are still under development, and highly unpredictable as taught by numerous teachings cited in Papers #9 and #17. The animal model may be acceptable for experimental test, but not well correlated with human diseases for reasons explained in Paper #17. Furthermore, it takes more than the

expression of a potentially therapeutic gene to achieve the goal of gene therapy, it requires long-term stable expression of the transgene in a significant population of appropriate cells and the appropriate response of the target cells to the transgene. These are some of the reasons why the promising potential of gene therapy has not met with the expectations in reality. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. Although the instant specification provides a brief review of a potential therapeutic use of the claimed vector and experimental studies, it is not enabled for its full scope because the specification does not disclose which genetic defective disease the method could be used to treat, any therapeutic effect in an established tumor, any therapeutic effect in an established *in vivo* infection, the lasting effects, the treatment regimen, etc. the cytotoxic effect is only one aspect that one would encounter to practice the claimed invention and would look for guidance in the specification. In summary, the teachings and guidance present in the specification, as a whole, represent an initial investigation into the feasibility of the development of a useful means for executing gene therapy for cancer and viral infection, which awaits further development to the practical level. Based upon the limited disclosure, the unpredictability of the art, the level of the skill, and the breadth of the claims, one skill in the art would have been required to perform undue experimentation to practice the invention.

Applicants further cite *Marzocchi* to argue that "it is incumbent upon the Patent Office wherever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertion of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. It is noted that *Marzocchi* also teaches "IN THE FIELD OF CHEMISTRY GENERALLY, THERE MAY BE TIMES **WHEN WELL-KNOWN UNPREDICTABILITY OF CHEMICAL REACTIONS WILL ALONE BE ENOUGH TO CREATE REASONABLE DOUBT** AS TO ACCURACY TO **BROAD STATEMENT** PUT FORWARD AS ENABLING SUPPORT FOR CLAIM; THIS WILL ESPECIALLY BE THE CASE WHERE STATEMENT IS, ON ITS FACE, CONTRARY TO

GENERALLY ACCEPTED SCIENTIFIC PRINCIPLES, ETC". When instant claims read on a method for the treatment of any disease associated with a genetic defect, cancer, and viral infections, a doubt is reasonable since there is no universal cure for these diseases as of today. Furthermore, the Office has provided numerous teachings such as *Verma, Orkin, Bowman,* and *Perez-Paya et al* to illustrate the state of the art and the levels of those skilled artisans to indicate the doubt is reasonable. Thus, it is applicants' duty to provide sufficient teaching to enable the claimed invention.

Moreover, applicants are reminded that 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970). In the many Office actions issued, the Examiner never requested human data for support, but indicated that the disclosure should be commensurate with the full scope of the claims. As indicated in the previous Office action, the specification fails to teach the therapeutic aspect for treating a genetic defect, the specification fails to identify or teach any genetic disease that could be treated by the claimed vector, and the specification fails to teach how to deliver the vector *in vivo* so that the vector could be targeted to the desired cells and the AMP peptides could be sufficiently expressed in the desired cells so that a therapeutic effect could be achieved. Thus, the specification fails to provide an enabling disclosure even showing that the cells in an animal were actually infected by the claimed vector.

Additionally, it is noted the in vivo data provided in the specification is an ex vivo gene therapy method, and the instant claims are drawn to in vivo gene therapy. The instant specification clearly teaches the differences of the two (Specification, page 5,

lines 3-21), and art known hurdles for practicing them. The specification clearly states the invention is to provide an in vivo method for gene therapy, yet, the only in vivo data is the ex vivo gene therapy method. Thus, the specification fails to provide an enabling disclosure commensurate with the scope of the claims.

The Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of any specific starting material **or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.
> Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Accordingly, for reasons of record and those set forth above, the instant specification fails to meet the enablement requirement.

## *Conclusion*

Claims 9-15, 20, 22, 26, 35-40, 46-48, 52, 60-65, 70-72, and 75 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
August 11, 2003

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER